AF/1617 #

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION: DALE R. LOVERCHECK

Serial No. 09/900,647 Art Unit:1617

Filed: July 7, 2001 Examiner: Hui, San Ming R.

For: UNIT DOSE OF MATERIAL IN SYSTEM AND METHOD

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

Fee Letter for Brief on Appeal

Submitted herewith in triplicate is Appellants Brief on Appeal in the above captioned patent application.

Enclosed is my check in the amount of $160.00 for filing this Brief on Appeal.

A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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March 10, 2003
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BRIEF ON APPEAL

(1) REAL PARTY IN INTEREST

The real party in interest is DALE R. LOVERCHECK.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

(3) STATUS OF CLAIMS

Claims 26-30, 33-35 and 37-46 are pending and on appeal.

Claims 1-25, 31, 32, 36 and 47 have been canceled.

(4) STATUS OF AMENDMENT

The amendment filed December 16, 2002 has been entered. It is the only amendment filed subsequent to the Final rejection dated November 26, 2002.

(5) SUMMARY OF THE INVENTION

A method of indication for a unit dose [see page 7, lines 4-8 (in this section citations refer to the above captioned patent application)] of an orally consumable material [see page 3, lines 11-19; and 24 and page 4, lines 1-6] for relief of discomfort [see page 4, line 12-17] and supplementing nutrition, [see page 3, lines 11-19; and page 6, line 3-15] comprising:

Enclosing a unit dose of orally consumable material in an enclosure. The unit dose comprising a predetermined amount of discomfort reliever [see page 4, line 18-20],

and a predetermined amount of at least one nutritional supplement [see page 6, line 3-7] selected from the group consisting of vitamin and mineral, and

Indicating the amount of the discomfort reliever in the unit dose, [page 7, lines 4-8]

Indicating the amount of the nutritional supplement in the unit dose, [page 7, lines 4-8]

Indicating a percent of a recommended daily value for the amount of the nutritional supplement in the unit dose, [see page 13, lines 1-11 and lines 21-24] and

Indicating that consumption of the unit dose provides relief for at least one discomfort selected from the group consisting of minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, insomnia, sleepiness, fatigue and drowsiness, [see page 4, line 12-17]

The discomfort reliever not being adapted to aid in or contribute to nutrition supplementing of the nutritional supplement, [see page 9, line 20-26 through page 10, line 1]

The nutritional supplement not being adapted to aid in or contribute to discomfort relieving of the discomfort reliever. The nutritional supplement not being adapted to aid in or contribute to reducing side effects of the discomfort reliever. [see page 8, lines 17-26 and page 9, line 1]

(6) ISSUES

Whether the claims are patentable over SS Pharmaceutical in view of Tsunoda, Yeh et al and Lambelet under 35 USC 103 [see page 4 of the Final rejection] with or without 21 CFR 201.57 see page 6 of the Final rejection (Exhibit A)].

(7) GROUPING OF THE CLAIMS

The claims are grouped together.

(8) ARGUMENT

THE APPLIED REFERENCES DO NOT DISCLOSE THE FEATURES OF THE CLAIMED INVENTION OR ANY BENEFIT FROM THE USE THEREOF

The court has held that the absence from the applied references of an explicit requirement of the claims makes the rejection improper, In re Evanega 4 USPQ 2nd 1249 (CAFC, 1987). All of the claims explicitly require a method of indication for supplementing nutrition, a nutritional supplement (as used in the above captioned patent

application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose. The applied prior art does not disclose supplementing nutrition, or any amount of vitamin that is a nutritional supplement, as used in the above captioned patent application. SS Pharmaceutical (lines 2-3 of the abstract), Tsunoda (lines 1-3 of the abstract) and Yeh et al (column 2, lines 5 and 31-37) disclose including antioxidant vitamins as part of a pharmaceutical medication (cold, menstruation and/or periodontal). The applied prior art references do not disclose or teach including any amount of antioxidant vitamins beyond that, which is part of a pharmaceutical medication (cold, menstruation and/or periodontal). Nor do the applied prior art references disclose or teach any amount of any antioxidant vitamin for supplementing nutrition. Additionally, the applied prior art do not disclose indicating a percent of a recommended daily value for any amount of the antioxidant portion of the pharmaceutical. The applied prior art pharmaceutical antioxidant vitamins are not disclosed as having a percent of a recommended daily value. So, one of ordinary skill in the pharmaceutical art would not indicate a percent of a recommended daily value for an antioxidant vitamin. All of the claims require nutritional supplement, as used in the above captioned patent application, which is not adapted to aid in or contribute to discomfort relieving of the discomfort reliever, or reducing side effects of the discomfort reliever. The applied references disclose antioxidant vitamins as being adapted to aid in or contribute to discomfort relieving functions of a pharmaceutical or to aid in or contribute to reducing side effects of the pharmaceutical. So, antioxidant vitamins as disclosed in the applied prior art are not nutritional supplements as used in the above captioned patent application because they are disclosed as being adapted to aid in or contribute to discomfort relieving functions of a discomfort reliever or to aid in or contribute to reducing side effects of the discomfort reliever. Thus, the applied prior art references do not disclose or teach a method of indication for supplementing nutrition, a nutritional supplement (as used in the above captioned patent application), or indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose, as claimed by Appellant. None of these explicit requirements of the claims are disclosed by SS Pharmaceutical, Tsunoda, Yeh et al or Lambelet [or 21 CFR 201.57 (Exhibit A)]. The absence from all of the applied references of these explicit requirements of claims 26-30, 33-35 and 37-46 makes the rejection erroneous and improper, In re Evanega. Accordingly, all of the claims are not unpatentable under 35

USC 103 over SS Pharmaceutical in view of Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

The Examiner states in the Advisory Action dated January 8, 2003 at page 2, that products of identical chemical compositions cannot have mutually exclusive properties, citing In re Spada and MPEP 2112.01. However, the applied prior art references do not disclose the chemical composition or properties of Appellant's claimed method. The applied prior art does not disclose nutritional supplement (as used in the above captioned patent application). Rather, applied prior art discloses antioxidant vitamins as part of pharmaceuticals, and thus as being adapted to aid in or contribute to discomfort relieving of the pharmaceuticals, or reducing side effects of the pharmaceuticals. So, the chemical composition of Appellant's claimed method is not identical to the chemical compositions of the applied prior art. Furthermore the antioxidant vitamins in the applied prior art are disclosed as being part of pharmaceuticals, as see Yeh et al column 2, lines 5 and 31-37. No amount of antioxidant vitamins is disclosed by the applied prior art as supplementing nutrition. Appellant's claims require nutritional supplement, which is in addition to antioxidant vitamin(s), if any, included in the discomfort reliever. Accordingly, the applied prior art, does not disclose a nutritional supplement as disclosed and claimed by Appellant. So, the applied prior art compositions are not identical to the chemical composition in Appellant's claims.

Additionally, the applied prior art does not provide the benefits of the invention. Beneficially, the invention provides the user with an indication of a percent of a recommended daily value for the amount of the nutritional supplement in each unit dose. With this indication the user has the ability to self regulate consumption of nutritional supplements while alleviating a discomfort.

ALL THE LIMITATIONS OF A CLAIM MUST BE CONSIDERED MEANINGFUL

All of the limitations of a claim must be considered meaningful, Perkin – Elmer Corp. v Westinghouse Elec. Corp. 3 USPQ2d 1321, 1324-25 (Fed. Cir, 1987). Appellant's claims require a method of indication for supplementing nutrition, a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose. These features are not disclosed by the applied prior art. A nutritional supplement, as used in the above captioned patent application, is not adapted to aid in or contribute to discomfort relieving functions of a discomfort reliever or to aid in or

contribute to reducing side effects of the discomfort reliever as do the antioxidant vitamins disclosed by the applied prior art. Nutritional supplement, as used in the above captioned patent application, is a new feature, in addition to the antioxidant vitamins disclosed in the applied prior art. Indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose is a new and additional feature, which is not disclosed in the applied prior art. All of the limitations of a claim must be considered meaningful, Perkin – Elmer Corp. The rejection does not meaningfully consider all of the limitations of the claims. Accordingly, the claims are not unpatentable over SS Pharmaceutical in view of Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

In the final rejection at page 5, the Examiner notes that Appellant's method claims enclosing a unit does of ibuprofen and vitamin C, and asserts the amount may be optimized. The applied prior art references disclose pharmaceuticals having antioxidant vitamins. So, the antioxidant vitamins are part of the pharmaceuticals disclosed by the applied prior art, and thus are adapted to aid in or contribute to discomfort relieving functions of the pharmaceutical or to aid in or contribute to reducing side effects of the pharmaceutical, as see Yeh et al, column 2, lines 5 and 31-37. And any optimization of antioxidant vitamins, as part of the pharmaceuticals disclosed by the applied prior art, would be for their antioxidant functions in the pharmaceuticals. While in the above captioned patent application nutritional supplements are in addition to the antioxidant vitamin agents disclosed in the applied prior art, which are adapted to aid in or contribute to discomfort relieving functions of a pharmaceutical or to aid in or contribute to reducing side effects of the pharmaceutical.

In the Advisory Action dated January 8, 2003 at page 2, the Examiner notes that ibuprofen and vitamin C are enclosed (in a dependent claim). The applied prior art discloses pharmaceuticals, which include antioxidant vitamins, as see Yeh et al, column 2, lines 5 and 31-37. These antioxidant vitamin(s) are disclosed as part of the pharmaceutical. Disclosure of an antioxidant vitamin as part of a pharmaceutical is not a disclosure of a nutritional supplement (as used in the above captioned patent application). Nor is it a basis for indicating a percent of a recommended daily value (or amount) of a nutritional supplement, as is required by all of Appellant's claims. As part of the pharmaceuticals, the antioxidant vitamins of the applied prior art are adapted to aid in or contribute to discomfort relieving functions of the pharmaceuticals or to aid in or contribute to reducing side effects of the pharmaceuticals. So, the antioxidant vitamin

part of a pharmaceutical of the applied prior art is not a nutritional supplement (as used in the above captioned patent application). Nutritional supplement (as used in the above captioned patent application) is in addition to the antioxidant vitamin part of a pharmaceutical. Thus, an amount of vitamin C in a nutritional supplement of Appellant's invention is in addition to an amount of antioxidant vitamin C as part of a pharmaceutical disclosed by the applied prior art. An amount of vitamin C in a nutritional supplement of Appellant's invention is indicated as a percent of a recommended daily value (or amount) of the nutritional supplement, as is required by all of Appellant's claims. The rejection is improper as it does not meaningfully consider all of the limitations of the claims, Perkin – Elmer. Accordingly, the rejection of claims 26-30, 33-35 and 37-46 as unpatentable over SS Pharmaceutical in view of Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)] is erroneous.

PATENTABILITY IS SUPPORTED BY A NEW AND UNOBVIOUS FUNCTIONAL RELATIONSHIP BETWEEN AN ENCLOSURE AND INDICATING

The Court has stated that patentability is supported by a new and unobvious functional relationship between an enclosure and indicating, Application of Miller 164USPQ 46, 49 (CCPA, 1969). Indicating may very well constitute limitations upon which patentability can be predicated, In re Royka and Martin 180 USPQ 580, 583 (CCPA, 1974). The applied prior art, does not disclose an enclosure enclosing a unit dose of discomfort reliever and having an indicator indicating a percent of a recommended daily amount of nutritional supplement (as used in the above captioned patent application) in the unit dose. Patentability of Appellant's claims is supported by a new and unobvious functional relationship between an enclosure enclosing a unit dose of discomfort reliever and indicating a percent of a recommended daily amount of nutritional supplement (as used in the above captioned patent application) in the unit dose, Application of Miller. Accordingly, the rejection of claims 26-30, 33-35 and 37-46 as unpatentable over SS Pharmaceutical in view of Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)] is erroneous.

SUPERIOR RESULTS

Benefits provided by the invention claimed in the above captioned patent application, which are not provided by the applied prior art include: a method of indication for supplementing nutrition, a nutritional supplement (as used in the

above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose. A practical significance of Appellant's invention, compared to the applied prior art, is that the user has an indication of a percent of a recommended daily value for the amount of the nutritional supplement in each unit dose. With this indication the user has the ability to self regulate consumption of nutritional supplements while alleviating a discomfort. This is a superior result. The statute does not require a patentable invention to be superior Demaco Corp v F Von Langsdorff Licensing Ltd. 7 USPQ2d 1222 (Fed. Cir 1988). The applied prior art discloses only amounts of antioxidant vitamins, which are adapted to aid in or contribute to discomfort relieving functions of a pharmaceutical or to reducing side effects of the pharmaceutical. Antioxidant vitamins are not nutritional supplements as used in the above captioned patent application. Appellant's claimed invention provides superior results by indicating a percent of a recommended daily value for the amount of the nutritional supplement and thereby providing the ability to self regulate nutritional benefits while alleviating a discomfort. Users of Appellant's claimed invention obtain the superior and additional feature of nutritional supplements, which are not adapted to aid in or contribute to discomfort relieving functions of a discomfort reliever or to aid in or contribute to reducing side effects of the discomfort reliever. Accordingly, the rejection of claims 26-30, 33-35 and 37-46 as being unpatentable over SS Pharmaceutical in view of Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)], is improper. Patentability is shown beyond the requirements of the statute.

THE APPLIED REFERENCES TEACH AWAY FROM THE INVENTION

The applied prior art discloses antioxidant vitamins as part of pharmaceuticals, as see SS Pharmaceutical (lines 2-3 of the abstract), Tsunoda (lines 1-3 of the abstract) and Yeh et al (column 2, lines 5 and 31-37). Disclosure of antioxidant vitamins as part of a pharmaceutical essentially teaches away from the invention, which requires a nutritional supplement in addition to a discomfort reliever. This is a per se demonstration of prima facie nonobviousness, In Re Dow Chemical Co. 5 USPQ 2d 1529 (CAFC), 1988. Accordingly, claims 26-30, 33-35 and 37-46 are not prima facie obviousness over the combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

The applied prior art discloses antioxidant vitamins as part of pharmaceutical medications (cold, menstruation and/or periodontal) without any disclosure of supplementing nutrition, or of indicating a percent of a daily recommended value for a nutritional supplement, as claimed by Appellant. This disclosure of antioxidant vitamins as part of pharmaceutical medications, (not for supplementing nutrition), essentially teaches away from the method of supplementing nutrition of the invention, and is a per se demonstration of prima facie nonobviousness, In Re Dow Chemical Co. Accordingly, claims 26-30, 33-35 and 37-46 are not prima facie obviousness over the combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

In the Advisory Action dated January 8, 2003 at page 3, the Examiner states that the Appellant has not pointed out exactly where the references teach away. The applied prior art discloses antioxidant vitamins are part of pharmaceuticals medications (cold, menstruation and/or periodontal) without any disclosure of supplementing nutrition, or of indicating a percent of a daily recommended value for a nutritional supplement, as see SS Pharmaceutical (lines 2-3 of the abstract), Tsunoda (lines 1-3 of the abstract) and Yeh et al (column 2, lines 5 and 31-37). Disclosure of antioxidant vitamins as part of a pharmaceutical is not a disclosure of supplementing nutrition, and thus is not in the field or pertinent to the problem with which Appellant's invention is involved. This direction to other fields without pertinence to the problem with which Appellant's invention is involved, essentially teaches away from the invention, which requires a nutritional supplement in addition to a discomfort reliever. This is a per se demonstration of prima facie nonobviousness, In Re Dow Chemical. Accordingly, claims 26-30, 33-35 and 37-46 are not prima facie obviousness over the combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

LACK OF ANY TEACHING FOR THE COMBINATION OF REFEREENCES

A proper combination of references requires a teaching in the references to suggest the combination thereof, In re Sernaker 702 F2d 989, 217 U.S.P.Q. 1 (CAFC, 1983). There is no teaching in SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)] to suggest the combination thereof to provide the method claimed by Appellant. SS Pharmaceutical discloses cold medication without any disclosure of menstruation or periodontal medication. Tsunoda discloses menstruation medication without any disclosure of cold or periodontal medication. Yeh et al discloses periodontal

medication without any disclosure of cold or menstruation medication. Lambelet discloses pharmaceuticals without any disclosure of cold, menstruation and/or periodontal medication. This lack of a showing of motivation for combining references cited in the rejection should result in reversal of the rejection In re Rouffet 47 USPQ2d 1453 (CAFC, 1998). Accordingly, the combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)] is improper, In re Semaker.

THE COMBINATION OF REFERENCES IS A HINDSIGHT RECONSTRUCTION OF APPELLANT'S INVENTION

In the Advisory Action dated January 8, 2003 at page 4, the Examiner states that so long as a reconstruction of the prior art takes into account only knowledge within the ordinary skill such is proper. A problem with the rejection is that nowhere in any reference (or 21 CFR 201.57 (Exhibit A)) is there any suggestion to indicate a percent of a recommended daily value for a nutritional supplement or to provide nutritional supplement indicated thereby. Appellant is the first to suggest indicating a percent of a recommended daily value for a nutritional supplement and providing nutritional supplement indicated thereby with a discomfort reliever. To say that this would have been obvious is to resort to impermissible hindsight, In re Marshall 198 USPQ 344 at 346-347 (CCPA, 1978).

Cold medication in SS Pharmaceutical, menstruation medication in Tsunoda, periodontal medication in Yeh et al and pharmaceuticals without any disclosure of cold, menstruation and/or periodontal medication in Lambelet are isolated disclosures. One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention. In re Fine, 837 F2d 1071, 1075, 5 USPQ 2d 1598, 1600 (Fed. Cir. 1988). The Examiner has picked and chosen among isolated disclosures in the prior art for cold medication, menstruation medication and periodontal disease medication and pharmaceuticals without any disclosure of cold, menstruation and/or periodontal medication. It is legal error to use the inventor's patent specification teaching of both a novel and nonobvious invention as though it were prior art in order to make claims appear to be obvious In re Pleuddemann, 901 F2d 823, 828, 15 USPQ 2d 1738, 1742 (Fed. Cir 1990). In constructing the final rejection the Examiner combines SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)] without any teaching in the references for the combination thereof. So, the

combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with and without 21 CFR 201.57 (Exhibit A)] in the final rejection is legal error.

YEH ET AL IS NONANALOGOUS ART

Yeh et al disclose medicine for periodontal disease (see column 1, lines 6-7 and column 2, lines 1-12). Periodontal disease is not a discomfort, and medicine for periodontal disease is not a discomfort reliever, as used in the above captioned patent application. The Examiner is in agreement that the instant claims are not drawn to treatment of disease, (see the Advisory Action dated January 8, 2003 at page 2). "Discomfort" is defined at page 4 in the above captioned patent application, to refer to discomfort from at least one of: minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, menstrual cramps, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, insomnia (difficulty in falling asleep), sleepiness, fatigue and drowsiness. These indications do not include periodontal disease, as is disclosed by Yeh et al. "Discomfort reliever" as used in the above captioned patent application, is defined at page 4 in the above captioned patent application, to refer to predetermined pharmaceutically effective amounts of orally consumable material adapted for temporary relief of at least one discomfort. Thus, discomfort reliever, as used in the above captioned patent application, refers to material adapted for temporary relief of at least one indication in the definition of discomfort. These indications do not include periodontal disease.

Yeh et al fails to qualify as analogous art under the Deminiski criteria of whether the art is in the same field (relieving discomfort, as used in the above captioned patent application, and supplementing nutrition) and reasonably pertinent to the particular problem with which the inventor is involved, (indicating a discomfort reliever, as used in the above captioned patent application and indicating a daily recommended amount of a nutritional supplement), In re Clay 23 USPQ 2d 1058, 1060 (1992, CAFC). Thus, Yeh et al is too remote to be treated as prior art, In re Sovish 769 F2d 738, 741; 226 USPQ 771, 773 (Fed.Cir., 1985). Yeh et al is directed to the field of medication for periodontal disease, see column 1, lines 6-7 and column 2, lines 1-12. Periodontal disease is not a discomfort as used in the above captioned patent application, see page 4, lines 12-17. Yeh et al disclose medication for periodontal disease. Yeh et al do not disclose a discomfort or supplementing nutrition as claimed by Appellant. Thus, Yeh et al do not

include disclosure in the field or disclosure pertinent to the problem with which Appellant is involved in the above captioned patent application. So, Yeh et al is not pertinent art, as Yeh et al is not part of the art to which the subject matter sought to be patented pertains Sovish. Thus, Yeh et al is too remote to be treated as prior art. Accordingly, the Examiner erred in his rejection of claims 26-30, 33-35 and 37-46 over the combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

THE REJECTION IS IMPROPER AS IT DOES NOT CONSIDER THE CLAIMED INVENTION OR THE REFERENCES AS A WHOLE.

Under 35 U.S.C. 103 (a) patentability is based on the differences between the subject matter sought to be patented and the prior art as a whole, MPEP 2141. As a whole the subject matter sought to be patented includes a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose. None of the applied prior art references discloses these features of the invention. Thus, the rejection fails to comply with the Office policy, to follow Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966), in the consideration and determination of obviousness under 35 USC 103 . The factual inquires enunciated by the Court in Graham for determining obviousness include: determining the scope and contents of the prior art; and ascertaining the differences between the prior art and the claims in issue. The contents of the applied prior art is void of a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose, as required by all of Appellant's claims. These requirements of all of Appellant's claims are ascertainable differences between the applied prior art and Appellant's claims.

When applying 35 USC 103 , the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir.

1986). The rejection is improper as it does not consider the claimed invention or the references as a whole. As discussed above at pages 2 through 4, some of the features of the invention are not disclosed by the applied prior art: a nutritional supplement (as used in the above captioned patent application), or indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose. The rejection is improper as the references do not suggest the desirability of making the combination, (see above at pages 8 and 9). The references are viewed with the benefit of impermissible hindsight vision afforded by the claimed invention; without a reasonable expectation of success, (see above at pages 7 and 8).

In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Schenck v. Nortron Corp., 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983), MPEP 2141.01. Both individually and collectively, the applied prior art references omit features of the invention, since none of them discloses a nutritional supplement (as used in the above captioned patent application), or indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose, as is required by all of Appellant's claims.

Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). The rejection disregards the claim requirements of providing a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose, as discussed above at pages 2 through 5. Disregarding limitations results in treating claims as though they read differently. Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447-49, 230 USPQ 416, 419-20 (Fed. Cir. 1986), MPEP 2141.01.

In the Advisory Action dated January 8, 2003 at page 3, the Examiner states that a chemical composition and its properties are inseparable. However, as discussed above at page 4, the applied prior art references do not disclose the chemical composition or properties of Appellant's claimed method. The applied prior art does not disclose nutritional supplement (as used in the above captioned patent application). Rather, applied prior art discloses antioxidant vitamins as part of pharmaceuticals, and thus as being adapted to aid in or contribute to discomfort relieving of the

pharmaceuticals, or reducing side effects of the pharmaceuticals. So, the chemical composition of Appellant's claimed method is not identical to the chemical compositions of the applied prior art. Furthermore the antioxidant vitamins in the applied prior art are disclosed as being part of pharmaceuticals, as see Yeh et al column 2, line 5. No amount of antioxidant vitamins is disclosed by the applied prior art as supplementing nutrition. Appellant's claims require nutritional supplement, which is in addition to antioxidant vitamin(s), if any, included in the discomfort reliever. Accordingly, the applied prior art, does not disclose a nutritional supplement as disclosed and claimed by Appellant. So, the applied prior art compositions are not identical to the chemical composition in Appellant's claims.

Furthermore, with regard to the Examiner's statement that a chemical composition and its properties are inseparable, in determining whether the invention as a whole would have been obvious under 35 USC 103 we must first delineate the invention as a whole. Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). It was not known in the pharmaceutical art prior to Appellant's invention, to include nutritional supplement in a discomfort reliever (as these terms are used in the above captioned patent application) or to indicate a percent of a recommended daily value for the amount of nutritional supplement. The invention provides a knowing and intended nutrition supplementing relationship between nutritional supplements and percent recommended daily amounts thereof provided. The invention provides new combinations of discomfort reliever products with a wide variety of nutritional supplements in recommended daily amounts for supplementing nutrition. This is an unexpected superior result, which is not disclosed in the applied prior art. Obviousness cannot be predicated on antioxidant vitamins, used as part of a pharmaceutical, which were not known or indicated for supplementing nutrition, even if some inherency of one of such features is later established, In re Rijckaert.

A prior art reference must be considered in its entirety, i.e., as a whole, including portions such as different purposes (for periodontal disease) and different functions (as antioxidants of a pharmaceutical composition), that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. The examiner has not produced a *prima facie* case, so the Appellant is under no obligation to submit evidence of nonobviousness. The

Examiner has resorted to "hindsight" based upon Appellant's disclosure, (see above at pages 7 and 8). The applied prior art does not disclose facts needed to show a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose, required by Appellant's claims (see above at pages 2 through 4). So, these facts, which are not disclosed in the applied prior art, cannot be gleaned from the applied prior art. Hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. See In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). MPEP 2142.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, in the references themselves, to modify the reference or to combine reference teachings; there must be a reasonable expectation of success, and the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellants disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The Examiner has not established a *prima facie* case of obviousness, as there is no suggestion or motivation, in the references themselves, to modify the reference or to combine reference teachings; there is no a reasonable expectation of success, and the prior art references do not teach or suggest all the claim limitations, (see above at pages 8 and 9). The Examiner has failed the initial burden to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). When the motivation to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. Ex parte Skinner, 2 USPQ2d 1788 (Bd. Pat. App. & Inter. 1986). The examiner must provide evidence which as a whole shows that the reference teachings establish a *prima facie* case of obviousness, which is more probable than not. The examiner has not shown that the reference teachings establish a *prima facie* case of obviousness, which is more probable than not.

Even if the combination of the references taught every element of the claimed invention, without a motivation to combine, the rejection is improper. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves. In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

The applied prior art, referred to as the basis for possessing a teaching, (at the paragraph bridging pages 5 and 6 of the Final rejection), does not mention, suggest or require supplementing nutrition, a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement in a unit dose. No provision appears in 21 CFR 201.57 (Exhibit A) for a nutritional supplement (as used in the above captioned patent application), and indicating a percent of a recommended daily value for the amount of the nutritional supplement. This lack of a nutritional supplement provision in the regulation of the pharmaceutical art reflects the absence of a teaching in the applied prior art for the combination thereof.

Thrice on page 5 of the Final rejection the Examiner states that modifications of the prior art to meet the claimed invention would have been within the ordinary skill of the art. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). A statement that modifications of the prior art to meet the claimed invention would have been within the ordinary skill of the art, because the references teach that some aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

The prior art cannot be modified or combined to reject claims as *prima facie* obvious unless there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) MPEP 2143.02 Ex parte Blanc, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)., MPEP 2143.03. The rejection does not include prior art showing a nutritional supplement (as used in the above captioned patent application), or indicating a percent of a recommended daily value for

the amount of the nutritional supplement in a unit dose, as required by all of Appellant's claims. The rejection does not amount to showing of *prima facie* obviousness of the claimed invention, as the applied prior art does not disclose all the claim limitations. The rejection does not amount to showing of *prima facie* obviousness of the claimed invention, as the applied prior art does not disclose a teaching or suggestion of the claim requirements missing from the applied prior art. "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 USC 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

The rejection is improper as it does not consider the claimed invention or the references as a whole. The rejection is improper as the references do not suggest the desirability of making the combination. The references are viewed with the benefit of impermissible hindsight vision afforded by the claimed invention; without a reasonable expectation of success. Accordingly, claims 26-30, 33-35 and 37-46 are not prima facie obviousness over the combination of SS Pharmaceutical, Tsunoda, Yeh et al and Lambelet [with or without 21 CFR 201.57 (Exhibit A)].

CONCLUSION

The prior art applied does not disclose the superior features or benefits of nutritional supplement, as claimed by Appellant, in a unit dose with a discomfort reliever (see above at pages 2-4 and 6-7). Indicating a percent daily recommended amount of a nutritional supplement in a discomfort reliever is a new, meaningful and additional feature, which is not disclosed in the applied prior art (see above at pages 2-4). All of the limitations of the claims must be considered meaningful (see above at pages 4-5). Patentability of Appellant's claims is supported by the meaningful and unobvious features of combining a nutritional supplement (as used in the above captioned patent application) and a discomfort reliever, and indicating a percent of a recommended daily amount of the nutritional supplement (see pages 4-5). The applied prior art references teach away from the invention by disclosure of antioxidant vitamins used as antioxidants in pharmaceuticals without any disclosure of supplementing nutrition (see above at pages 7-8). The applied prior art references lack any teaching for the combination thereof (see above at page 9). None of the applied references discloses a use in common with any other applied reference (see above at page 8). The applied

combination of references is based upon improper hindsight reconstruction of Appellant's invention (see above at page 9). The claims are patentable over the nonanalogous applied prior art: Yeh et al (see above at pages 9-10). The rejection is improper as it does not consider the claimed invention as a whole (see above at pages 11-16). The claimed invention as a whole requires features not disclosed in the applied prior art. The rejection is improper as it does not consider each reference as a whole. None of the applied prior art references discloses a nutritional supplement (as used in the above captioned patent application), or indicating a percent of a recommended daily amount of nutritional supplement, as required by the claimed invention as a whole (see above at pages 11-16).

Reversal of the Final Rejection and allowance of the claims is respectfully requested.

Respectfully submitted,

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APPENDIX

26. (Amended) A method of indication for a unit dose of an orally consumable material for relief of discomfort and supplementing nutrition, comprising:

enclosing a unit dose of orally consumable material in an enclosure, said unit dose comprising a predetermined amount of discomfort reliever, and a predetermined amount of at least one nutritional supplement selected from the group consisting of vitamin and mineral, and

indicating said amount of said discomfort reliever in said unit dose,

indicating said amount of said nutritional supplement in said unit dose,

indicating a percent of a recommended daily value for said amount of said nutritional supplement in said unit dose, and

indicating that consumption of said unit dose provides relief for at least one discomfort selected from the group consisting of minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, insomnia, sleepiness, fatigue and drowsiness,

said discomfort reliever not being adapted to aid in or contribute to nutrition supplementing of said nutritional supplement,

said nutritional supplement not being adapted to aid in or contribute to discomfort relieving of said discomfort reliever , said nutritional supplement not being adapted to aid in or contribute to reducing side effects of said discomfort reliever.

27. The method of claim 26 wherein said nutritional supplement is vitamin C and said discomfort reliever is ibuprofen.

28. The method of claim 26 wherein said nutritional supplement comprises at least 50 mg of vitamin C and said discomfort reliever comprises at least 50 mg of ibuprofen.

29. The method of claim 26 further comprising providing an indicator and wherein said indicator indicates that consumption of said unit dose provides temporary relief for at least two discomforts selected from the group consisting of minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, sleepiness, fatigue and drowsiness.

30. The method of claim 26 further comprising providing an indicator and wherein said indicator indicates that consumption of said unit dose provides temporary relief for at least three

discomforts selected from the group consisting of minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, sleepiness, fatigue and drowsiness.

32. (Amended) The method of claim 26 wherein said nutritional supplement is a functional nutritional supplement and said discomfort reliever is a functional discomfort reliever selected from the group consisting of ibuprofen, naproxen, caffeine and acetaminophen.

33. The method of claim 26 wherein said container has an indicator with indications for consuming said unit dose for pain relief, and for supplementing nutrition.

34. (Amended) The method of claim 26 wherein said unit dose is formed into a pill, tablet or capsule.

35. The method of claim 26 wherein said indicating is provided by an indicator supported by said enclosure.

37. The method of claim 26 wherein said discomfort is headache.

38. (Amended) A method of indication for a unit dose of an orally consumable material for relief of discomfort and supplementing nutrition, comprising:

enclosing a unit dose of orally consumable material, in an enclosure having an indicator, said unit dose comprising a predetermined amount of discomfort reliever, and a predetermined amount of at least one nutritional supplement selected from the group consisting of vitamin, mineral and herb,

said indicator indicating said amount of said discomfort reliever in said unit dose,

said indicator indicating said amount of said nutritional supplement in said unit dose, said indicator indicating a percent of a recommended daily amount of said nutritional supplement in said unit dose, and said indicator indicating that consumption of said unit dose provides relief for at least one discomfort selected from the group consisting of minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, insomnia, sleepiness, fatigue and drowsiness,

said discomfort reliever not being adapted to aid in or contribute to nutrition supplementing of said nutritional supplement,

said nutritional supplement not being adapted to aid in or contribute to discomfort relieving functions of said discomfort reliever , said nutritional supplement not being adapted to aid in or contribute to reducing side effects of said discomfort reliever.

39. The method of claim 38 wherein said nutritional supplement is vitamin C and said discomfort reliever is ibuprofen.

40. The method of claim 38 wherein said indicator indicates that consumption of said unit dose provides temporary relief for at least two discomforts selected from the group consisting of minor aches and pain associated with a common cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, sleepiness, fatigue and drowsiness.

41. The method of claim 38 wherein said nutritional supplement is selected from the group consisting of vitamin and mineral, and said discomfort reliever is selected from the group consisting of ibuprofen, naproxen, caffeine and acetaminophen.

42. (Amended) The method of claim 38 wherein said indicator is supported by said enclosure and said unit dose is formed into a pill, tablet or capsule.

43. The method of claim 38 wherein said unit dose of an orally consumable material comprises at least 50 mg of said nutritional supplement and at least 50 mg of said discomfort reliever.

44. (Amended) A method of indication for a unit dose of an orally consumable material for temporary relief of discomfort and for supplementing nutrition with a nutritional supplement, comprising:

enclosing a unit dose of orally consumable material, in an enclosure having an indicator, said unit dose comprising a predetermined amount of discomfort reliever, and a predetermined amount of at least one nutritional supplement selected from the group consisting of vitamin, mineral and herb,

said unit dose comprising at least 50 mg of said nutritional supplement and at least 50 mg of said discomfort reliever,

said indicator indicating said amount of said discomfort reliever in said unit dose,

said indicator indicating said amount of said nutritional supplement in said unit dose, said indicator indicating a percent of a recommended daily amount for said amount of said nutritional supplement in said unit dose, and said indicator indicating that consumption of said unit dose provides temporary relief for at least one discomfort selected from the group consisting of minor aches and pain associated with a common

cold, headache, toothache, backache, muscular aches, minor pain of arthritis, fever, running nose, sneezing, itching of nose or throat, itchy watering eyes due to hay fever or other upper respiratory allergy, insomnia, sleepiness, fatigue and drowsiness,

said discomfort reliever not being adapted to aid in or contribute to nutrition supplementing of said nutritional supplement,

said nutritional supplement not being adapted to aid in or contribute to discomfort relieving functions of said discomfort reliever , said nutritional supplement not being adapted to aid in or contribute to reducing side effects of said discomfort reliever.

45. (Amended) The method of claim 44 wherein said nutritional supplement is vitamin C and said discomfort reliever is ibuprofen, said unit dose has a form selected from the group consisting of pill, tablet, and capsule.

46. The method of claim 26 wherein said discomfort is sleepiness, fatigue or drowsiness.

EXHIBIT A

[Code of Federal Regulations] [Title 21, Volume 4] [Revised as of April 1, 2002] From the U.S. Government Printing Office via GPO Access [**CITE: 21CFR201.57**] [Page 21-31] TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED) PART 201--LABELING--Table of Contents Subpart B--Labeling Requirements for Prescription Drugs and/or Insulin Sec. 201.**57** Specific requirements on content and format of labeling for human prescription drugs. Each section heading listed in Sec. 201.56(d), if not omitted under Sec. 201.56(d)(3), shall contain the following information in the following order: (a) Description. (1) Under this section heading, the labeling shall contain: (i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug; (ii) The type of dosage form and the route of administration to which the labeling applies; (iii) The same qualitative and/or quantitative ingredient information as required under Sec. 201.100(b) for labels; (iv) If the product is sterile, a statement of that fact; (v) The pharmacological or therapeutic class of the drug; (vi) The chemical name and structural formula of the drug; (vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics. (2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated. (b) Clinical Pharmacology. (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information. (2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well- controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances: (i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement ``The following in vitro data are available but their clinical significance is unknown.'' (ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in Sec. 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under Sec. 201.58 or Sec. 314.126(b) of this chapter. (c) Indications and Usage. (1) Under this section heading, the labeling shall state that: (i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or (ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or (iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or (iv) The drug, if used for a particular indication only in conjuction with a [[Page 22]] primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy. (2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in Sec. 314.126(b) of this chapter unless the requirement is waived under Sec. 201.58 or Sec. 314.126(b) of this chapter. (3) This section of the labeling shall also contain the following additional information: (i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in Sec. 314.126(b) of this chapter unless the requirement is waived under Sec. 201.58 or Sec. 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the ``Dosage and Administration'' section of the labeling and referenced in this section. (ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section. (iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use. (iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition. (v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in Sec. 314.126(b) of this chapter unless this requirement is waived under Sec. 201.58 or Sec. 314.126(b) of this chapter. (d) Contraindications. Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state ``None known.'' (e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning

as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the ``Indications and Usage'' section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is [[Page 23]] associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the ``Adverse Reactions'' section of the labeling. (f) Precautions. Under this section heading, the labeling shall contain the following subsections as appropriate for the drug: (1) General. This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling. (2) Information for patients. This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the ``Precautions'' section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in Sec. 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling. (3) Laboratory tests. This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy. (4)(i) Drug interactions. This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the ``Dosage and Administration'' section of the labeling rather than under this subsection of the labeling. (ii) Drug/laboratory test interactions. This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests. (5) Carcinogenesis, mutagenesis, impairment of fertility. This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the ``Warnings'' section of the labeling. [[Page 24]] Also, under ``Precautions,'' the labeling shall state: ``See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility.'' (6) Pregnancy. This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information: (i) Teratogenic effects. Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category: (a) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: ``Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: ``Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug).'' The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child. (b) Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well- controlled studies in pregnant women, the labeling shall state: ``Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.'' If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: ``Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child. (c) Pregnancy category C. If animal

reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well- controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: ``Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the [[Page 25]] fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well- controlled studies in humans, the labeling shall state: ``Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child. (d) Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: ``Pregnancy Category D. See `Warnings' section.'' Under the ``Warnings'' section, the labeling states: ``(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus." (e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: ``Pregnancy Category X. See `Contraindications' section.'' Under ``Contraindications,'' the labeling shall state: ``(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinant animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus." (ii) Nonteratogenic effects. Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease. (7) Labor and delivery. If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown. (8) Nursing mothers. (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described. (ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: ``Because of the potential [[Page 26]] for serious adverse reactions in nursing infants from (name of drug) (or, ``Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: ``Caution should be exercised when (name of drug) is administered to a nursing woman.'' (iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: ``It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (name of drug) (or, ``Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: ``It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman.'' (9) Pediatric use. (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents. (ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the ``Indications and Usage'' section of the labeling, and appropriate pediatric dosage information shall be given under the ``Dosage and Administration'' section of the labeling. The ``Pediatric use'' subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the ``Clinical Pharmacology'' or ``Clinical Studies'' section. As appropriate, this information shall also be contained in the ``Contraindications,'' ``Warnings,'' and elsewhere in the ``Precautions'' sections. (iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the ``Pediatric use'' subsection of the labeling and discussed in

more detail, if appropriate, under the ``Clinical Pharmacology'' and ``Clinical Studies'' sections. Appropriate pediatric dosage shall be given under the ``Dosage and Administration'' section of the labeling. The ``Pediatric use'' subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the ``Contraindications,'' ``Warnings,'' and elsewhere in the ``Precautions'' sections. (iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have [[Page 27]] concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the ``Pediatric use'' subsection of the labeling shall contain either the following statement, or a reasonable alternative: ``The safety and effectiveness of (drug name) have been established in the age groups -- to -- (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).'' Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the ``Clinical Pharmacology'' or the ``Clinical Studies'' section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the ``Clinical Pharmacology'' section. Pediatric dosing instructions shall be included in the ``Dosage and Administration'' section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the ``Pediatric use'' subsection and, as appropriate, in the ``Contraindications,'' ``Warnings,'' ``Precautions,'' and ``Dosage and Administration'' sections. (v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the ``Pediatric use'' subsection of the labeling shall contain an appropriate statement such as ``Safety and effectiveness in pediatric patients below the age of (- -) have not been established.'' If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ``Contraindications'' or ``Warnings'' section of the labeling and this subsection shall refer to it. (vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: ``Safety and effectiveness in pediatric patients have not been established.'' If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ``Contraindications'' or ``Warnings'' section of the labeling and this subsection shall refer to it. (vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate. (viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric [[Page 28]] subgroups, a special note of this risk shall be made, generally in the ``Contraindications,'' ``Warnings,'' or ``Precautions'' section. (10) Geriatric use. (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the ``Indications and Usage'' section of the labeling, and appropriate geriatric dosage shall be stated under the ``Dosage and Administration'' section of the labeling. The ``Geriatric use'' subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the ``Geriatric use'' subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under ``Clinical Pharmacology'' or the ``Clinical Studies'' section. As appropriate, this information shall also be contained in ``Contraindications,'' ``Warnings,'' and elsewhere in ``Precautions.'' (ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the ``Geriatric use'' subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The ``Geriatric use'' subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information: (A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the ``Geriatric use'' subsection shall include the following statement: ``Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of

decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy." (B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the ``Geriatric use" subsection shall contain the following statement: Of the total number of subjects in clinical studies of (name of drug), -- percent were 65 and over, while -- percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. (C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or [[Page 29]] effectiveness, or requires specific monitoring or dosage adjustment, the ``Geriatric use" subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the ``Contraindications," ``Warnings," ``Dosage and Administration," or other sections of the labeling. (iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the ``Geriatric use" subsection of the labeling and in detail under the ``Clinical Pharmacology" section. The ``Clinical Pharmacology" section and ``Drug interactions" subsection of the ``Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs. (B) If a drug is known to be substantially excreted by the kidney, the ``Geriatric use" subsection shall include the statement: ``This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function." (iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the ``Geriatric use" subsection of the labeling, or, if appropriate, the hazard shall be stated in the ``Contraindications," ``Warnings," or ``Precautions" section of the labeling, and the ``Geriatric use" subsection shall refer to those sections. (v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that: ``Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely." (vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate. (g) Adverse Reactions. An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. (1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. (2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: ``The most frequent adverse reaction(s) to (name of drug) is (are) (list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur [[Page 30]] rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in Sec. 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists. (3) The ``Warnings" section of the labeling or, if appropriate, the ``Contraindications" section of the labeling shall identify any potentially fatal adverse reaction. (4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in Sec. 314.126(b) of this chapter unless this requirement is waived under Sec. 201.58 or Sec. 314.126(b) of this chapter. (h) Drug Abuse and Dependence. Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug: (1) Controlled Substance. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated. (2) Abuse. This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified. (3) Dependence. This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described. (i) Overdosage. Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following: (1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug. (2) Complications that can occur with the drug (for example, organ toxicity or

delayed acidosis). (3) Oral LD<INF>50</INF> of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the ``Clinical Pharmacology'' section also may be referenced here, if applicable to overdoses. (4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening. (5) Whether the drug is dialyzable. (6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use. (j) Dosage and Administration. This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual [[Page 31]] duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: ``Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.'' (k) How Supplied. This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include: (1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation; (2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100; (3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and (4) Special handling and storage conditions. (l) Animal Pharmacology and/or Animal Toxicology. In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used. (m) ``Clinical Studies'' and ``References''. These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under Secs. 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the ``Clinical Studies'' or ``References'' section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions: (1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under Sec. 314.126(b) of this chapter. (2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug. [44 FR 37462, June 26, 1979, as amended at 55 FR 11576, Mar. 29, 1990; 59 FR 64249, Dec. 13, 1994; 62 FR 45325, Aug. 27, 1997; 63 FR 66396, Dec. 1, 1998] [[Page 32]]